ANTI-GM-CSF ANTIBODIES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Continuation of U.S. application Ser. No. 15/386,152, filed Dec. 21, 2016, which is a Continuation of U.S. application Ser. No. 12/923,363, filed Sep. 16, 2010, which is a Divisional of U.S. application Ser. No. 11/914,599, which is the US National Stage application of PCT/EP2006/004696, filed May 17, 2006, which claims priority from U.S. Provisional Application 60/682,009, filed May 18, 2005. The entire contents of each of the aforementioned applications are incorporated herein by reference.

[0002] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-WEB and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Jun. 13, 2019, is named sequence.txt and is 61,479 bytes.

BACKGROUND OF THE INVENTION

[0003] Granulocyte-macrophage colony stimulating factor, GM-CSF, was originally identified as a hemopoietic growth factor. It is produced by a number of cell types including lymphocytes, monocytes, endothelial cells, fibroblasts and some malignant cells (Metcalf et al., 1986; Clark and Kamen, 1987; Hart et al., 1988; Metcalf et al., 1986). In addition to having a function of growth stimulation and differentiation on hemopoietic precursor cells, GM-CSF also was discovered as having a variety of effects on cells of the immune system expressing the GM-CSF receptor (for review see: Hamilton, 2002; de Groot et al., 1998). The most important of these functions is the activation of monocytes, macrophages and granulocytes in several immune and inflammatory processes (Gasson et al., 1990b; Gasson et al., 1990a; Hart et al., 1988; Rapoport et al., 1992).

[0004] Mature GM-CSF is a monomeric protein of 127 amino acids with two glycosylation sites. The variable degree of glycosylation results in a molecular weight range between 14 kDa and 35 kDa. Non-glycosylated and glycosylated GM-CSF show similar activity in vitro (Cebon et al., 1990). The crystallographic analysis of GM-CSF revealed a barrel-shaped structure composed of four short alpha helices (Diederichs et al., 1991). The overall folding is similar to other growth factors like growth hormone, interleukin-2 and interleukin-4.

[0005] GM-CSF exerts its biological activity by binding to its receptor (Kastelein and Shanafelt, 1993; Sisson and Dinarello, 1988). The most important sites of GM-CSF receptor (GM-CSF-R) expression are on the cell surface of myeloid cells and endothelial cells, whereas lymphocytes are GM-CSF-R negative. The native receptor is composed of at least two subunits, alpha and beta. The alpha subunit imparts ligand specificity and binds GM-CSF with nanomolar affinity (Gearing et al., 1989; Gasson et al., 1986). The beta subunit is also part of the interleukin-3 and interleukin-5 receptor complexes and, in association with the GM-CSF receptor alpha subunit and GM-CSF, leads to the formation of a complex with picomolar binding affinity (Hayashida et al., 1990). The binding domains on GM-CSF for the receptor have been mapped: GM-CSF interacts with the beta subunit of its receptor via a very restricted region in the first alpha helix of GM-CSF (Shanafelt et al., 1991b; Shanafelt et al., 1991a; Lopez et al., 1991). Binding to the alpha subunit could be mapped to the third alpha helix, helix C, the initial residues of the loop joining helices C and D, and to the carboxyterminal tail of GM-CSF (Brown et al., 1994).

[0006] Formation of the GM-CSF trimeric receptor complex leads to the activation of complex signaling cascades involving molecules of the JAK/STAT families, Shc, Ras, Raf, the MAP kinases, phosphatidylinositol-3-kinase and NFkB, finally leading to transcription of c-myc, c-fos and c-jun. Activation is mainly induced by the beta subunit of the receptor (Hayashida et al., 1990; Kitamura et al., 1991; Sato et al., 1993). The shared beta subunit is also responsible for the overlapping functions exerted by IL-3, IL-5 and GM-CSF (for review see: de Groot et al., 1998).

[0007] Apart from its hemopoietic growth and differentiation stimulating activity, GM-CSF functions especially as a proinflammatory cytokine. Macrophages and monocytes as well as neutrophils and eosinophils become activated by GM-CSF, resulting in the release of other cytokines and chemokines, matrix degrading proteases, increased HLA expression and increased expression of cell adhesion molecules or receptors for CC-chemokines. The latter, in turn, leads to increased chemotaxis of inflammatory cells into inflamed tissue (Chantry et al., 1990; Hamilton, 2002; Sisson and Dinarello, 1988; Zhang et al., 1998; Hamilton et al., 1993; Lopez et al., 1986; Cheng et al., 2001; Gomez-Cambronero et al., 2003). Often, GM-CSF exerts its activity in synergy with other inflammatory stimulating factors like other cytokines or LPS, e.g. neutrophils treated with GM-CSF in combination with e.g. LPS will show increased oxidative burst (Kaufman et al., 1989; Rapoport et al., 1992).

[0008] GM-CSF as Target for Anti-Inflammatory Therapy:

[0009] Due to its diverse activating functions in the immune system, GM-CSF can be considered as a target for anti-inflammatory therapy. Chronic and acute inflammatory diseases like rheumatoid arthritis (RA), multiple sclerosis (MS), Crohn's disease, psoriasis, asthma, atopic dermatitis or shock may well benefit from the blocking of GM-CSF activity and subsequent reduction of harmful activities of GM-CSF responsive cells (Hamilton, 1993; Zhang et al., 1998; Hamilton, 2002).

[0010] Arthritis:

[0011] Several groups showed that GM-CSF, as well as its receptor, are present in the synovial joint of arthritis patients (Alvaro-Gracia et al., 1991; Xu et al., 1989; Haworth et al., 1991). Additionally, GM-CSF was shown to cause flares of rheumatoid arthritis in patients treated with GM-CSF for neutropenia in Felty's syndrome (Hazenberg et al., 1989) or after chemotherapy (de Vries et al., 1991).

[0012] First hints on the usefulness of antibodies blocking GM-CSF for the treatment of arthritis came from mouse in vivo studies (Campbell et al., 1997; Campbell et al., 1998; Cook et al., 2001). Specifically, Cook et al. showed that neutralizing antibodies to GM-CSF showed efficacy in a collagen-induced arthritis model. Blocking of GM-CSF led to a reduction of disease severity concerning inflammation, cartilage destruction and progression of disease in initially affected limbs or progression to other limbs.

[0013] There are several effects of an anti-GM-CSF therapy from which the patients with rheumatoid arthritis or with other inflammatory diseases could benefit.